Managing side effects of cancer immunotherapy for the acute physician

ABSTRACT

Immunotherapy is a novel type of anti-cancer treatment that works by upregulating the host's immune system to fight against cancer cells. Landmark immunotherapy trials have demonstrated improvements in response rates and survival compared to cytotoxic chemotherapy. Specific immunotherapies known as checkpoint inhibitors are now routinely used in a range of cancers including melanoma, lung, renal and urological cancers. Immunotherapies are associated with immune-related adverse events which are very different to those seen with traditional cytotoxic chemotherapies. This can present a new challenge to oncologists, acute physicians and the wider team of health-care professionals who look after patients receiving immunotherapy. Generally, these side effects are easily managed but some, if untreated, can be subtle and potentially life-threatening. Patients on immunotherapy may present to a wide variety of medical professionals including the emergency department, primary care and general medical admissions units. It is therefore vital that there is increased awareness and education to identify and manage side effects of immunotherapy effectively.

In recent years, there have been many advances in oncology with a marked increase in treatment options available including chemotherapy, hormone therapy, targeted treatments and immunotherapy. Checkpoint inhibitors, a type of immunotherapy, are now used for the treatment of many cancers including melanoma, lung, renal, bladder, prostate, and head and neck cancers. In this article, all references to immunotherapy relate to checkpoint inhibitors.

Immunotherapies have revolutionized the treatment of many types of cancer, most notably melanoma. However, immunotherapy has a different side-effect profile to cytotoxic chemotherapy agents and knowledge of this is paramount to aid early recognition and management of potentially serious toxicities. An understanding of how immunotherapy works can help further appreciate its side effects. The immune system is normally involved in identifying and eliminating cancer cells. However, cancer cells can 'avoid' this through an array of complex of interactions with the tumour microenvironment. The body's immune response to cancer cells can be increased by blocking inhibitory signals, also known as 'immune checkpoints', delivered to the host T-cells. The main therapeutic targets in immunotherapy are the CTLA-4 (cytotoxic T-lymphocyte-associated protein 4) and PD-1 (programmed cell death protein 1) pathways (*Table 1*).

Since checkpoint inhibitors work by prolonging T-cell activation, they can lead to systemic loss of immune tolerance resulting in the development of immune-related adverse events. The presentation of immune-related adverse events is vast and can affect multiple organ systems including the skin, gastrointestinal tract, endocrine organs, liver and lungs. Immunotherapy can also exacerbate pre-existing autoimmune conditions, in particular rheumatological conditions. The most commonly observed immune-related adverse events are skin-related toxicities, such as rash and pruritus. Generally, these can be managed conservatively with emollients, steroid creams and antihistamines but they may rarely be severe enough to require systemic steroids (e.g. involving >30% body surface area).

Dr Benjamin A Pickwell-Smith, Specialist Registrar in Medical Oncology, Department of Oncology, Lancashire Teaching Hospitals NHS Trust, Fulwood, Preston

Mr Alfred CP So, Medical Student, Faculty of Biology, Medicine and Health, University of Manchester, Manchester

Dr Ruth E Board, Consultant Medical Oncologist, Department of Oncology, Lancashire Teaching Hospitals NHS Trust, Fulwood, Preston PR2 9HT and Honorary Senior Lecturer Faculty of Biology, Medicine and Health, University of Manchester, Manchester

Correspondence to: Dr RE Board (ruth.board@lthtr.nhs.uk)

Table 1. Current immune checkpoint inhibitor drugs approved by National Institute for Health and Care Excellence (NICE)

Target	Drug (trade name)	Indications for use
CTLA-4	Ipilimumab (Yervoy)	Metastatic melanoma (single agent and in combination with nivolumab)
PD-1	Nivolumab (Opdivo)	Metastatic melanoma, non-small-cell lung cancer, renal cancer, head and neck cancer, relapsed or refractory classical Hodgkin's lymphoma
	Pembrolizumab (Keydruda)	Melanoma, non-small cell lung cancer, urothelial cancer
PD-L1	Atezolizumab (Tecentriq)	Non-small cell lung cancer, urothelial cancer
	Avelumab (Bavencio)	Merkel cell cancer
	Durvalumab (Imfinzi)	Not yet NICE approved

CTLA-4 = cytotoxic T-lymphocyte-associated protein 4; PD1 = programmed cell death protein 1; PDL1 = programmed cell death ligand 1

This article focuses on the recognition and management of four important immune-related adverse events that can present in the acute take: colitis, hypophysitis, pneumonitis and hepatitis. It is important to remember that immune-related adverse events can present in any organ system and it is therefore vital to have a low threshold for any acute presentation of a patient receiving immunotherapy. Physicians should involve the acute oncology service as soon as possible and refer to any local guidelines for early management. Most of the recommendations detailed in this article are based on the UK Oncology Nursing Society (2018) and European Society of Medical Oncology (Haanen et al, 2017) guidelines.

When to contact the acute oncology team

Patients may present with immunotherapy-related problems at any time, including many months after treatment has been discontinued. All patients with a suspected or confirmed immune-related adverse event should be discussed as soon as possible with the local acute oncology service, and with the treating oncology team within 24 hours (UK Oncology Nursing Society, 2018). Rarely, side effects of immunotherapy can be life-threatening, so practitioners should contact the acute oncology service as soon as possible. In severe cases, referral to the appropriate specialist is advised (e.g. endocrinologist). In cases of mild immune-related adverse events, management may be conservative with timely discharge and appropriate follow up. Oncologists and specialist nurses aim to educate patients about the possible side effects of immunotherapy and urge patients to inform health-care professionals that they are not receiving cytotoxic chemotherapy. Despite this, some patients refer to their treatment as 'chemotherapy' and it is therefore essential to enquire about the exact type of treatment the patient is receiving.

Immune-related colitis

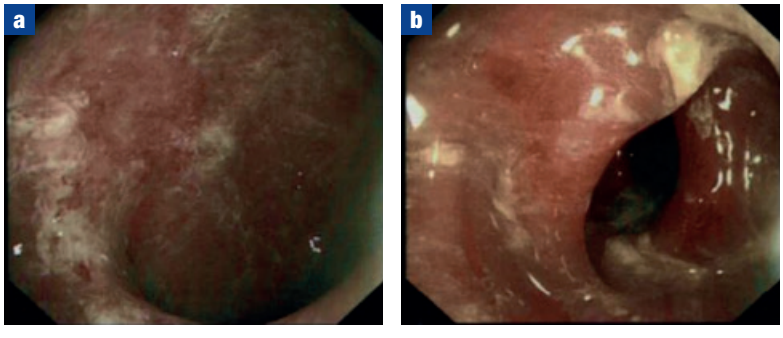
Approximately one third of patients treated with anti-CTLA-4 agents have gastrointestinal side effects including aphthous ulcers, oesophagitis, gastritis, diarrhoea and colitis (Ibrahim et al, 2011). Beck et al (2006) reported an overall incidence of enterocolitis in 21% of patients receiving ipilimumab. Colonic perforation has been observed in patients receiving ipilimumab, with an incidence of 0.7% and 6.6% for patients with melanoma and renal cell carcinoma respectively (Beck et al, 2006). In a phase 3 trial of ipilimumab in patients with metastatic melanoma, three patient deaths were attributed to colitis (Eggermont et al, 2016). Onset of colitis may occur any time during treatment and has been reported several months after receiving the last dose of treatment (Lord et al, 2010). Gastrointestinal toxicity is also well described in patients receiving combined anti-CTLA-4 and anti-PD-1 antibodies, with reported incidences of diarrhoea and colitis at 44.1% and 11.8% respectively (Larkin et al, 2015). These immune-related adverse events are less common with anti-PD-1 antibodies with the incidences of diarrhoea and colitis around 19.2% and 1.3% respectively (Larkin et al, 2015).

> **"Patients may present with immunotherapy-related problems at any time, including many months after treatment has been discontinued."**

The most common symptom of immune-related colitis is diarrhoea but other symptoms may include abdominal pain, haematochezia, weight loss, fever and vomiting (Marthey et al, 2016). The important differential diagnoses are infection and gastrointestinal metastases. Initial investigations are needed to exclude infectious causes and assess for complications of colitis. Blood tests should be performed for full blood count, urea and electrolytes, liver function tests and C-reactive protein. Stool samples should be sent for microscopy, culture, viral studies and *Clostridium difficile* toxin. Levels of faecal calprotectin can be measured as these may be raised in patients with colitis (Marthey et al, 2016). Abdominal X-ray or computed tomography scan should also be considered to rule out perforation and toxic megacolon. In moderate–severe cases, or if symptoms persist in mild cases despite treatment, endoscopic evaluation should be considered. In a case series of anti-CTLA-4 induced colitis, the rectum and sigmoid colon were most commonly involved (Marthey et al, 2016). Endoscopic appearances consist of erythema, erosions and/or ulceration (*Figures 1a* and *b*). Chronic inflammatory changes have also been observed on endoscopy and biopsy several months after the onset of enterocolitis (Marthey et al, 2016).

Management of immune-related diarrhoea and colitis is based on severity (Haanen et al, 2017). Grade 1 is defined as passage of fewer than four loose stools per day. Treatment is supportive with anti-diarrhoeal agents and fluids, and immunotherapy can usually be continued. If symptoms persist (i.e. longer than 14 days) then oral prednisolone

Figure 1. A 55-year-old patient presented with grade 3 diarrhoea after three cycles of pembrolizumab for metastatic melanoma. a. Colonoscopy demonstrated extensive moderate erythema and granularity in the rectum. Histological examination revealed an increase in chronic inflammatory cells; the overall appearances were similar to collagenous colitis. b. An area extending from the distal sigmoid to the proximal sigmoid demonstrating extensive moderate erythema and granularity.



> “Pneumonitis is a rare but potentially life-threatening immune-related adverse event associated with immunotherapy.”

0.5–1 mg/kg should be started. Grade 2 toxicity is defined as passage of four to six loose stools a day or presence of other symptoms such as nocturnal diarrhoea, mucus in stools, abdominal pain or nausea. Immunotherapy should be withheld temporarily while the diarrhoea is investigated and treated. Supportive measures should be implemented with anti-diarrhoeal medication. If symptoms persist beyond 3 days, oral prednisolone 0.5–1 mg/kg should be commenced.

If adverse signs such as dehydration, fever, tachycardia or haematochezia are present, or if the patient is experiencing more than six loose stools a day (grade 3 diarrhoea), the patient should be admitted to hospital for high-dose steroids. A surgical review should be considered in cases of severe diarrhoea with adverse features. If there is no improvement by 72 hours or the condition is worsening, infliximab 5 mg/kg can be used provided there is no contraindication. There is a lack of evidence for the use of other immunosuppressants in this situation. Early involvement of the local gastroenterology team is recommended. Patients with bowel perforation require emergency colectomy.

Immune-related hypophysitis

Hypophysitis (inflammation of the pituitary gland) can occur with immunotherapy. Rates of incidence vary depending on the class of immunotherapy and whether combination treatment was used. Larkin et al (2015) reported an incidence of 7.7% with combination ipilimumab plus nivolumab. It is a rare side effect with anti-PD-1 or anti-PD-L1 (programmed cell death ligand 1) antibodies alone (Torino et al, 2016). It has been reported that 1% of patients with metastatic melanoma treated with nivolumab have hypophysitis (Wolchok et al, 2017). Presentation of hypophysitis can be varied with vague symptoms such as headaches, visual disturbance, fatigue, altered consciousness, deranged electrolytes (especially hyponatraemia), anorexia and mood changes. It is important to consider hypothyroidism, hypoadrenalism and pan-hypopituitarism in patients who are unwell on immunotherapy. Investigation and management should be instituted promptly. Patients should be assessed using the ‘ABCDE’ approach with consideration of other differential diagnoses including brain metastasis, leptomeningeal disease or cerebrovascular disease.

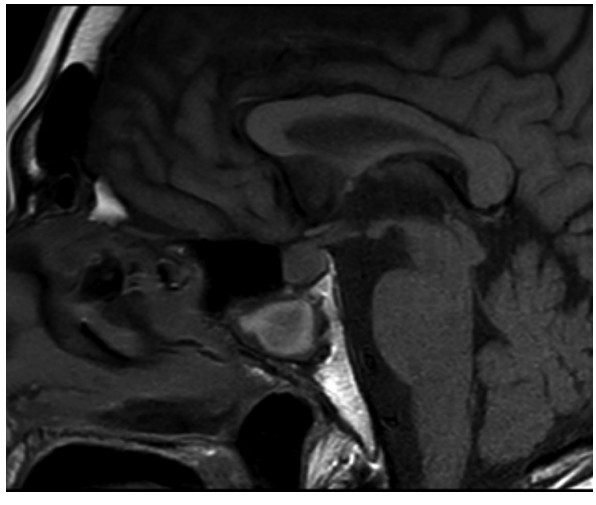
An endocrine panel should be performed to include thyroid function tests, follicle-stimulating hormone, luteinizing hormone, testosterone (in men), oestradiol (in premenopausal women), prolactin and insulin-like growth factor. A 9am cortisol level should be ideally taken or a random cortisol if the patient is unwell and treatment cannot be delayed. A 9am cortisol <250 nmol/litre or random cortisol <150 nmol/litre is consistent with hypoadrenalism and indicates a need to treat with hydrocortisone replacement. Steroid replacement should be initiated in suspected cases of moderate to severe hypophysitis after sending off endocrine function tests. A magnetic resonance imaging pituitary scan should be performed and may reveal an enlarged pituitary gland that can also resemble a metastatic lesion (*Figure 2*).

Once the diagnosis has been confirmed, the acute oncology team or treating cancer unit should be updated. Treatment decisions should be made in collaboration with an endocrinologist, ideally a clinician with experience in this area. If the patient is clinically well, then immunotherapy may be continued. Hormone replacement should be promptly initiated based on local protocols. Patient education is key with specific emphasis on ‘sick day rules’ and use of intra-muscular steroids. It is important to recognize that autoimmune endocrinopathies are a permanent side effect of immunotherapy and patients need to be aware of this risk and the need for lifelong hormone replacement.

Immune-related pneumonitis

Pneumonitis is a rare but potentially life-threatening immune-related adverse event associated with immunotherapy. A meta-analysis of 20 anti-PD-1 therapy trials in advanced cancers reported an incidence of any-grade pneumonitis of 2.7% (Nishino et al, 2016). Incidence of grade ≥3 pneumonitis is rare but deaths associated with pneumonitis have been reported (Ahn et al, 2015; Naidoo et al, 2017). Furthermore, deaths from opportunistic infections associated with immunosuppressive treatment of pneumonitis have also been observed (Naidoo et al, 2017). The clinicopathological features of immune-

Figure 2. A 65-year-old man received two cycles of ipilimumab and presented with dizziness, hypotension and hyponatraemia. A magnetic resonance imaging pituitary scan was initially reported as showing heterogeneous contrast enhancement suggestive of metastasis. On further review this was confirmed to be hypophysitis consistent with the clinical picture and undetectable cortisol levels.



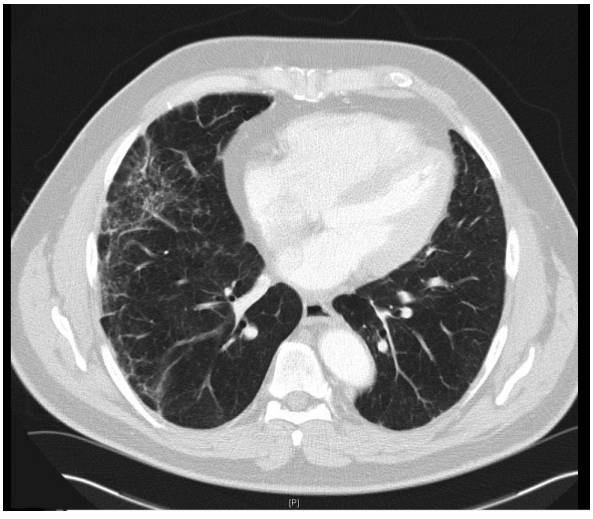
related pneumonitis are similar to those of interstitial lung disease and can vary in their presentation. While some patients can rapidly decompensate from respiratory failure, around a third of patients are asymptomatic at onset (Naidoo et al, 2017). Median time to onset of symptoms is 2.8 months (range 9 days to 19.2 months) with the most common symptoms being dyspnoea (53%), cough (35%), fever (12%) and chest pain (7%) (Naidoo et al, 2017).

Immune-related pneumonitis is more common with certain treatment regimens, tumour types and patient comorbidities. Combination treatment with anti-PD-1 and anti-CTLA-4 therapy resulted in a higher incidence and earlier presentation of pneumonitis compared with anti-PD-1 monotherapy (Naidoo et al, 2017; Nishino et al, 2016). Patients with non-small-cell lung cancer and renal cell cancer have higher incidences of any-grade pneumonitis compared with melanoma (Nishino et al, 2016). A meta-analysis comparing anti-PD-1 with anti-PD-L1 therapies observed a higher incidence of any-grade and grade ≥3 pneumonitis with anti-PD-1 therapies (P<0.05) (Khunger et al, 2017). Unsurprisingly, patients with a pre-existing lung condition (e.g. asthma, chronic obstructive pulmonary disease), current or ex-smokers, or previous exposure to thoracic radiation are also at a higher risk of pneumonitis (Ahn et al, 2015; Naidoo et al, 2017).

The diagnosis of immune-related pneumonitis can be difficult and common cardiopulmonary conditions should be excluded (e.g. pneumonia, pulmonary oedema, pulmonary embolism, cardiac disease). Recommended baseline investigations include a chest X-ray, full blood workup (including full blood count, urea and electrolytes, liver function tests, thyroid function tests, calcium, erythrocyte sedimentation rate, C-reactive protein), sputum samples, and screening for opportunistic infections (Haanen et al, 2017). High-resolution computed tomography scan is the preferred imaging for pneumonitis. Radiological features may include ground glass opacities (37%), hypersensitivity pneumonitis (22%) and cryptogenic organizing pneumonia (19%) (*Figure 3*) (Naidoo et al, 2017). Other important differentials include progression of disease and immune-related granulomatosis disease (e.g. sarcoidosis). Bronchoscopy with biopsy and/or bronchioalveolar lavage may be required in symptomatic patients where a diagnosis of an acute infection or disease progression cannot be excluded. In grade 3–4 pneumonitis, atypical infections should be excluded. This may involve β-D-glucan and galactomannan for systemic fungal infections, urinary legionella and pneumococcal antigens, mycoplasma serology and *Pneumocystis jirovecii* pneumonia screening (UK Oncology Nursing Society, 2018).

The management of immune-related pneumonitis is primarily based on expert opinion and small observational studies (Haanen et al, 2017; UK Oncology Nursing Society, 2018). Patients with grade 1 pneumonitis are clinically asymptomatic with only radiographical changes. These patients can be managed conservatively by monitoring their symptoms every 2–3 days and immunotherapy can be continued. Grade 2 pneumonitis is further characterized by mild to moderate symptoms limiting instrumental activities of daily living. Treatment involves oral prednisolone 0.5–1.0 mg/kg/day and deferral of immunotherapy. If an infection cannot be safely ruled out before administration of immunosuppressants (i.e. steroids), concurrent coverage with broad-spectrum antibiotics is recommended.

Figure 3. A 60-year-old man with metastatic melanoma presented with a cough after four cycles of pembrolizumab. Computed tomography scan demonstrated extensive sub-pleural interstitial changes in both lungs consistent with pneumonitis. He was treated with oral prednisolone with good clinical response.



If symptoms do not improve with treatment after 48 hours, patients are managed as grade 3–4 pneumonitis. Grade 3–4 pneumonitis is described as severe symptoms limiting activities of daily living, hypoxia and/or acute respiratory distress syndrome. Hospital admission and escalation of care is required with intravenous methylprednisolone 2–4 mg/kg/day (or dose equivalent), oxygen therapy (if hypoxaemic), permanent discontinuation of immunotherapy and broad-spectrum antibiotics.

Early involvement of the local respiratory team is recommended. Additional immunosuppressive regimens (e.g. infliximab, myocophenolate mofetil, cyclophosphamide) should be considered if the patient does not improve after 48 hours. An analysis of the phase 1 KEYNOTE-001 trial, in patients with advanced non-small-cell lung cancer treated with pembrolizumab, showed that 76.2% cases of pneumonitis can be effectively managed with high-dose steroids alone (Ahn et al, 2015). Early discussions with the patient and the intensive care unit are important to determine the ceiling of care. As immunotherapies move into the adjuvant setting these conversations are increasingly important as pneumonitis is a reversible side effect.

KEY POINTS

- Immune-related adverse events can vary in presentation and onset.
- Prompt recognition and management of immunotherapy side effects is vital.
- Initial treatment for moderate to severe immune-related toxicities is with oral or intravenous high-dose steroids.
- Early involvement of the acute oncology team is required in all cases.

Immune-related hepatitis

Hepatitis is a less common but important immune-related adverse event associated with immunotherapy. It occurs in 6–7% of patients with advanced melanoma receiving either anti-PD-1 or anti-CTLA-4 therapy and up to 30% of those receiving combination ipilimumab and nivolumab therapy (Larkin et al, 2015). A meta-analysis of 17 trials in different tumour types demonstrated that anti-CTLA-4 treatments have a higher risk of any-grade and grade ≥3 hepatotoxicity compared with anti-PD-1 treatments (Wang et al, 2017). Furthermore, they showed that patients with melanoma were at a higher risk of hepatotoxicity compared to other tumour types. The presence of liver metastasis does not appear to increase the risk of hepatotoxicity (Huffman et al, 2017).

The clinical presentation of immune-related hepatitis is variable. It is often asymptomatic and diagnosed on routine blood tests. Generalized derangement of liver function tests or isolated rises in specific liver markers (e.g. alanine transaminase) may be the presenting feature. A retrospective single-centre study in patients with advanced melanoma showed that the most common presenting feature of immune-related hepatitis was fatigue (Huffman et al, 2017). The median time to onset of any-grade immune-related hepatitis was 52 days (range 16–152 days) (Huffman et al, 2017). Jaundice has also been observed as an initial presenting feature of immune-related hepatitis in the emergency department (Doherty et al, 2017).

In patients with suspected immune-related hepatitis, a liver screen should be performed to rule out infectious causes (hepatitis A, B, C, E serologies, cytomegalovirus and Epstein–Barr virus serology), autoimmune disease (ANA, anti-SMA, anti-LKM, anti-SLA, anti-LP, anti-LCI), and metabolic (iron studies) causes of hepatitis (Haanen et al, 2017). A full history will help exclude other causes of drug-induced hepatitis (e.g. paracetamol overdose, alcohol). Other initial blood tests include full blood count, liver function tests, conjugated and unconjugated bilirubin, clotting screen, lactate, amylase and creatinine kinase. An ultrasound scan should be considered in the first 12–24 hours to assess for splenomegaly and hepatic vasculature (UK Oncology Nursing Society, 2018). Further imaging such as magnetic resonance imaging of the liver and a liver biopsy may be necessary, particularly if the hepatitis is unresponsive to initial steroid treatment.

Patients with grade 1 hepatitis (aspartate transaminase or alanine transaminase level >upper limit of normal to 3 x upper limit of normal) can continue on checkpoint inhibitors with regular monitoring of their liver function tests. Grade 2 hepatitis is defined as aspartate transaminase or alanine transaminase level 3–5 x upper limit of normal). Treatment involves prednisolone 1 mg/kg/day and deferral of checkpoint inhibitors and hepatotoxic drugs (e.g. paracetamol, non-steroidal anti-inflammatory drugs, statins). If liver function tests do not improve on treatment after 72 hours, then manage as grade 3–4 hepatitis. Patients with grade 3–4 hepatitis should be admitted to the hospital with urgent referral to the hepatologist. Grade 3 hepatitis (aspartate transaminase or alanine transaminase level >5x upper limit of normal) requires treatment with either oral prednisolone 1 mg/kg/day (if aspartate transaminase or alanine transaminase level ≤400 IU/litre) or intravenous hydrocortisone 100–200 mg four times a day (if aspartate transaminase or alanine transaminase level >400 IU/litre) while grade 4 hepatitis (aspartate transaminase or alanine transaminase level >20x upper limit of normal) requires intravenous methylprednisolone 2 mg/kg/day. N-acetylcysteine and antibiotic prophylaxis should also be considered. In steroid-refractory hepatitis, myocophenolate mofetil is recommended as the second-line immunosuppressive treatment (Haanen et al, 2017; UK Oncology Nursing Society, 2018).

Conclusions

Immunotherapy treatments are used in oncology with increasing indications for different tumour types. Their use has changed the landscape of cancer treatment with dramatic improvements in outcomes. However, this treatment is associated with a wide range of immune-related adverse e vents that can vary in presentation and onset. While this article only focussed on specific immune-related adverse events, other important rare toxicities to be aware of include interstitial nephritis, neurological conditions (e.g. myasthenia gravis, Guillain–Barré syndrome) and ocular toxicities (e.g. iritis, uveitis).

Generally, patients receiving immunotherapy who present in an emergency setting should be suspected of having an immune-related adverse event. Prompt recognition of this can potentially help initiate early life-saving steroid treatment. Although a non-specialist may be hesitant about using high-dose steroids in patients with cancer, the use of common immunosuppressive treatments for immune-related adverse events do not appear to affect overall survival (Horvat et al, 2015). It is also important to recognize that high-dose steroid treatment for immune-related adverse events is often administered long term and may result in opportunistic infections, osteoporosis and adrenal suppression.

Early referral to the acute oncology team and treating oncologist is warranted in all cases of suspected immune-related adverse events and may be necessary to involve other specialties in severe cases. Finally, refer to any local or international guidelines for immune-related adverse events if there is any doubt about their initial management (Haanen et al, 2017; UK Oncology Nursing Society, 2018). BJHM

Conflict of interest: Dr RE Board has received educational grants and honoraria from Bristol Myers Squibb and Merck Sharp & Dohme; Dr BA Pickwell-Smith and Mr ACP So: none.

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